

Warfarin-induced Venous Limb Gangrene

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ABSTRACT

Warfarin is a commonly used anticoagulant that has been associated with several significant cutaneous side effects, most notably warfarin-induced skin necrosis. A lesser known adverse reaction to warfarin is warfarin-induced venous limb gangrene. Both cutaneous adverse effects share the same pathophysiology, but are clinically quite different. The majority of cases of warfarin-induced venous limb gangrene has been in patients with cancer or heparin-induced thrombocytopenia. However, other hypercoagulable disease states, such as the antiphospholipid antibody syndrome, can be associated with venous limb gangrene. In order to increase recognition of this important condition, the authors report a case of warfarin-induced venous limb gangrene in a patient with presumed antiphospholipid antibody syndrome and review the literature on warfarin-induced venous limb gangrene. (*J Clin Aesthet Dermatol.* 2012;5(11):38–42.)

Warfarin is a commonly used anticoagulant that has been associated with several significant cutaneous side effects. The authors report a case of warfarin-induced venous limb gangrene in a patient with presumed antiphospholipid antibody syndrome (APS). Warfarin-induced venous limb gangrene is a distinct entity from warfarin-induced skin necrosis. Due to its infrequency and the fact that it presents much differently than warfarin-induced skin necrosis, physicians may dismiss the fact that warfarin is the cause of a patient's necrosis. For this reason, it is important to recognize this as a separate clinical disease from warfarin-induced skin necrosis with similar underlying pathophysiology. This report of warfarin-induced venous limb gangrene is intended to increase the index of suspicion for this rare drug reaction whose effective treatment requires early diagnosis.

CASE REPORT

A 45-year-old man with a history of deep vein thrombosis (DVT) and pulmonary embolus (PE) presented to his local hospital with bilateral foot pain. He was immediately transferred to the university hospital for treatment of cyanotic toes concerning for bilateral critical limb ischemia. The patient's medical history included chronic obstructive pulmonary disease, alcohol abuse,

seizure disorder, atrial fibrillation, and nonischemic cardiomyopathy. Notably, three months prior to presentation, he had been hospitalized with a large DVT and PE. He had an inferior vena cava filter placed and was prescribed warfarin therapy. The patient's other home medications included phenytoin, diltiazem, and an albuterol inhaler.

On arrival to the hospital, the patient was admitted to the medical intensive care unit due to altered mental status and acute respiratory failure requiring intubation and mechanical ventilation. The patient's international normalized ratio (INR) at admission was 14.1 (normal 0.8–1.2), PTT was 46 seconds (normal 24–34 seconds), and platelets were 74,000/ μ L (normal 150,000–450,000/ μ L). Warfarin was held and vitamin K and fresh frozen plasma were administered. Vascular surgery personnel assessed the patient on arrival and did not find any evidence for critical limb ischemia. Easily palpable bilateral dorsalis pedis and posterior tibial pulses were found on exam. Dermatology was then consulted for assessment of the patient's toes.

On dermatological exam, sharply defined, confluent, noninflammatory irregular purpura were present involving all 10 toes, bilateral distal dorsal feet, and bilateral distal soles with several overlying large hemorrhagic bullae (Figures 1A–1C). Additional tense intact hemorrhagic and nonhemorrhagic bullae on nonerythematous base were

DISCLOSURE: The authors report no relevant conflicts of interest.

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noted on otherwise uninvolved more proximal foot and ankle. There was no appreciable livedo reticularis. Palpable pulses were noted in bilateral lower extremities. Hands were not involved.

A lower extremity Duplex ultrasound demonstrated acute right lower extremity thrombus within the common femoral, profunda femoral, femoral, popliteal, and proximal calf veins. A partially occlusive mid to distal left femoral vein thrombosis was identified as well. Skin biopsy from an area of purpura on the right foot demonstrated thrombotic vasculopathy with nonspecific direct immunofluorescence. Vascular channels in the superficial dermis were congested and occasional intravascular fibrin thrombi were present. Additional labs were remarkable for a positive lupus anticoagulant and anticardiolipin immunoglobulin M (IgM, 20.4 MPL units; normal ≤ 12.5). A heparin platelet aggregation assay was normal. A transthoracic echocardiogram did not reveal mural thrombi or valvular vegetations.

On further questioning, the authors learned the patient had been admitted to his local hospital three months prior with unprovoked DVT and PE. At that time, he had an inferior vena cava filter placed and was started on warfarin. It was suspected that the patient was not caring for himself or taking warfarin as prescribed so he was referred to a home health nursing agency. One week prior to this hospital admission, a home health nurse began administering warfarin without concurrent low molecular weight heparin.

The patient was subsequently diagnosed with acute bilateral lower extremity venous limb gangrene associated with a supratherapeutic INR on warfarin in the context of likely antiphospholipid antibody syndrome. He had a history of an unprovoked DVT, PE, and one set of positive antiphospholipid antibodies. Warfarin was held and both vitamin K and fresh frozen plasma administered due to documentation of an active hypercoagulable state. He was also placed on enoxaparin for long-term anticoagulation and was stabilized medically. He ultimately underwent bilateral transmetatarsal amputations. He did not return 12 weeks later for repeat antiphospholipid antibody testing.

DISCUSSION

Warfarin-induced venous limb gangrene and skin necrosis are both a reflection of a relatively hypercoagulable state created by initiation of warfarin therapy. Warfarin inhibits the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X.¹ However, it also inhibits production of natural anticoagulant proteins C and S, which have a shorter half-life than the clotting factors. Therefore, proteins C and S are depleted first, resulting in a relatively hypercoagulable state during the initial 24 to 48 hours of warfarin therapy.

Warfarin-induced skin necrosis is necrosis of central skin and subcutaneous tissue typically overlying areas with significant adipose tissue, such as the breast, abdomen, thigh, or buttocks.^{2,3} It usually occurs in the first

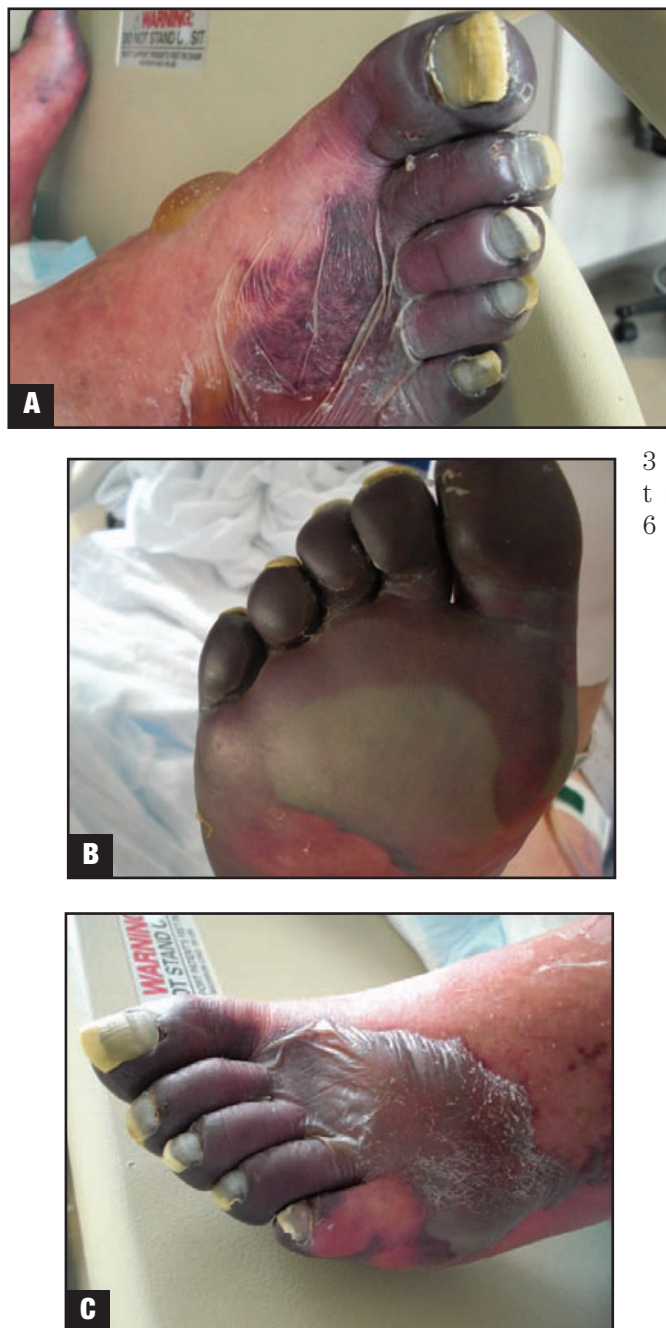


Figure 1. Warfarin-induced venous limb gangrene may present with sharply defined, noninflammatory, irregular purpura and hemorrhagic bullae as seen in the patient described in this case. (A) Right dorsal foot, (B) right sole of foot, (C) left dorsal foot.

days after beginning therapy.² Warfarin-induced skin necrosis is seen more commonly in patients with congenital protein C deficiency, which increases susceptibility to this complication.⁴

Venous limb gangrene was first described by Warkentin⁵ as limb necrosis despite palpable or Doppler-identifiable arterial pulses.⁵ Warkentin stated that the limb necrosis was a result of DVT progression in the setting of a supratherapeutic INR.⁵ As opposed to warfarin-induced

TABLE 1. Review of patients with warfarin-induced venous limb gangrene reported in the current literature

PATIENT	PRESENTATION AND SEQUELAE	INR
24yoF with SLE and HIT ⁴	PE and painful, purpuric lesions on bilateral calves that progressed to full-thickness necrosis requiring skin grafts	6.1
34yoF with HIT ³	Right lower limb DVT and thrombosis of left axillary vein causing pain, swelling, and cyanosis of left hand, which resolved with treatment	4.0
35yoF with HIT ³	Left lower limb DVT leading to venous gangrene of entire left foot requiring below knee amputation. Also developed central skin necrosis	7.2
49yoF with HIT ³	Left lower limb DVT leading to venous limb gangrene of distal left foot requiring below knee amputation	7.2
50yoF with HIT ⁴	DVT of right arm and rapidly progressive cyanosis mandating alteplase for two days. Also developed warfarin-induced skin necrosis of left breast	4.5
50yoF with adenocarcinoma ¹⁴	Right lower extremity DVT leading to skin necrosis on lateral aspect of right shin and ankle and early gangrene of 2nd and 3rd toes	4.5
55yoF with HIT after coronary artery bypass surgery ⁴	Right leg DVT developing into cyanosis, which resolved with treatment	5.8
56yoF with HIT ³	Bilateral lower extremity DVTs and PE resulting in necrosis of 8 toes. Healing occurred without amputation	9.4
59yoF with HIT ²	Right calf DVT leading to extension of thrombus and cyanosis of right foot resulting in right above knee amputation. The patient also developed warfarin-induced skin necrosis. She died of multi-system organ failure	9.6
61yoF with recent aortic valve replacement, Raynaud's phenomenon ¹⁵	Necrosis of multiple digits following valve replacement. DVT of right superficial and femoral and right popliteal veins leading to necrosis affecting 7 fingers and 10 toes. No amputation required	4.3
62yoF with HIT after cardiac surgery ¹⁶	DVT leading to distal tissue sloughing; amputation was not required	7.3
66yoF with metastatic lung cancer and suspected HIT ⁵	Right femoral DVT leading to necrosis. The patient died of respiratory failure	7.2
71yoF with HIT ¹⁷	Swelling, pain, cyanosis, and mottling of lower extremity and multiple bilateral PE. No improvement of cardiopulmonary status or of leg. Patient died	NS
72yoF with atrial fibrillation and recent coronary artery bypass surgery ⁴	Pain and discoloration of left breast, right leg, and left foot. Venous leg lesions progressed, requiring below the knee amputation of right leg and left transmetatarsal amputation	6.4
80yoF with HIT ¹⁸	Bilateral DVTs leading to bilateral venous limb gangrene that resolved with treatment	NS
Present patient, 45yoM with likely APS	Bilateral lower extremity DVTs leading to cyanosis of 10 toes with purpura and hemorrhagic bullae of feet eventually requiring bilateral transmetatarsal amputations	14.1
52yoM with gastric adenocarcinoma ¹³	Left lower extremity DVT and violaceous, bullous exanthem on the dorsal lateral left foot, which progressed to gangrene	8.8
53yoM with lung adenocarcinoma ¹⁹	PE and bilateral popliteal DVT leading to venous limb gangrene of left leg and skin necrosis of right leg. No amputation required	14.5
58yoM with HIT ⁴	DVT of femoral vein and PE. Also with warfarin-induced skin necrosis of thigh leading to sepsis and death	4.0
82yoM with HIT ¹⁶	Bilateral lower extremity DVT, which led to lower limb ischemia and gangrene requiring bilateral below-knee amputations	5.9

Abbreviations: yoF=year-old female; yoM=year-old male; SLE=systemic lupus erythematosus; HIT=heparin-induced thrombocytopenia; PE=pulmonary embolus; DVT=deep venous thrombosis; NS=not stated; APS=antiphospholipid syndrome

skin necrosis, venous limb gangrene begins distally in an extremity and progresses proximally.⁶ Although a supratherapeutic INR may seem to signify high levels of anticoagulation, in the first days of warfarin use it actually represents a state of relative hypercoagulability. The supratherapeutic INR in the setting of venous limb gangrene is a surrogate marker for depressed protein C activity.⁵ The INR represents a depleted factor VII level, which, due to similar half-lives of the proteins, correlates with the depression of protein C.⁵ At the same time, the levels of thrombin-antithrombin complexes in patients with warfarin-induced venous limb gangrene have been found to be elevated.⁵ When activated, protein C decreases the amount of thrombin produced by proteolyzing factors Va and VIIIa.⁹ Warfarin treatment of conditions associated with increased thrombin generation, such as cancer, heparin-induced thrombocytopenia (HIT), and the antiphospholipid antibody syndrome, may lead to microvascular thrombosis, venous thrombosis without arterial involvement, and warfarin-induced limb gangrene.^{3,7,8} Interestingly, patients with congenital protein C deficiency who are at high risk for warfarin-induced skin necrosis are not at increased risk for warfarin-induced venous limb gangrene.

Although most cases of venous limb gangrene in the literature developed in patients with cancer or HIT, APS is also an acquired risk factor for DVT and therefore for venous limb gangrene.⁹ The cases of warfarin-induced venous limb gangrene in the literature are presented in Table 1. All patients reported in the literature with warfarin-induced venous limb gangrene had a hypercoagulable state, DVT, and supratherapeutic INR. It is postulated that DVTs lead to venous limb gangrene by either direct propagation of the DVT from larger, deep veins to smaller, distal vessels and venules or by blood flow reduction to the affected limb.²

The patient reported in this case was found to likely have antiphospholipid antibody syndrome. APS is an autoimmune disorder defined by a propensity for venous and/or arterial thrombosis or recurrent fetal loss in the presence of either antiphospholipid antibodies or lupus anticoagulant antibodies.¹⁰ The diagnostic criteria for APS include at least one clinical and one laboratory criteria.¹¹ The clinical criteria consist of vascular thrombosis defined as either one or more episodes of arterial, venous, or small vessel thrombosis or a complication of pregnancy including three or more unexplained consecutive spontaneous abortions before the tenth week of pregnancy, one spontaneous abortion of morphologically normal fetus after the tenth week of pregnancy, or premature birth before 34 weeks.¹¹ The laboratory criteria consist of an elevated anticardiolipin, lupus anticoagulant, or anti-beta-2-microglobulin antibodies on at least two occasions at least 12 weeks apart.¹¹ It is hypothesized that the antiphospholipid antibodies cause direct endothelial injury and platelet activation as well as interfering with the protein C, antithrombin, and fibrinolytic pathways.¹⁰

Antiphospholipid antibodies may vary over time, but levels have been shown to remain stable for at least 75 percent of future tests.¹² The variation seen has not been shown to be associated with medications, such as warfarin, but transient antiphospholipid antibodies have been noted in the presence of infection.¹² The combination of APS and a supratherapeutic INR-associated depressed protein C level yielded a markedly prothrombotic milieu, which eventuated in bilateral venous limb gangrene in the patient described in this case.

The treatment of venous limb gangrene varies depending on the reason for the patient's hypercoagulable state. First, warfarin should be discontinued as it is the causative agent. In addition, due to the hypercoagulable state of the patient, an alternative anticoagulant is necessary.¹³ The patient described in this case was given vitamin K and fresh frozen plasma to overcome the effects of warfarin on protein C. He was also placed on enoxaparin for long-term anticoagulation. In summary, it is important for clinicians to have a high index of suspicion for this rare drug reaction since effective treatment requires early diagnosis.

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